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EXAMINER				
LUCAS, ZACHARIAH				
ART UNIT		PAPER NUMBER		
1648				

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding..

## Office Action Summary

Application No.

09/981,636

Applicant(s)

MARKS ET AL

Examiner

Zachariah Lucas

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-15 and 73-93 is/are pending in the application.
- 4a) Of the above claim(s) 4, 73-76, 80, 82, 90, 91 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-15, 77-79, 81, 83-89, 92 and 93 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 3-7-05.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### DETAILED ACTION

1. Currently, claims 1-15 and 73-93 are pending in the application. In the prior action, mailed on November 5, 2004, claims 1-72 were pending, with claims 4 and 16-72 withdrawn as to nonelected inventions and claims 1-3 and 5-15 rejected. In the Response filed on March 3, 2005, claims 1, 2, 6-12, 14, and 15 were amended; claims 16-72 were cancelled; and new claims 73-92 were added.

2. Newly submitted claims 73 and 74 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: these claims read on the claimed methods wherein the non-covalent bonding between the reporter and the antibody ligand is through a metal chelation bond. Originally, the claims identified only one means of such non-covalent bonding, bonding through an epitope tag. See, claim 8. This prior presentation is considered to be an election by original presentation, and the newly added alternatives to this means of non-covalent bonding are withdrawn as to non-elected species, there being no allowable generic claim.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 73 and 74 stand withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 75, 76, 80, 82, 90, and 91 are withdrawn as to non-elected inventions. In the Response of August 2004, the Applicant elected embodiments of the claimed invention wherein

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the reporter/effector is a fluorescent label. The indicated claims require the use of other types of labels, and therefore do not fall within the scope of the elected inventions.

3. Currently, claims 1-3, 5-15, 77-79, 81, 83-89, 92, and 93 are under examination to the extent that they read on the elected inventions, or are generic thereto.

***Information Disclosure Statement***

4. The Matzku et al. reference, cited in the July 11, 2003 IDS, has been considered.

***Claim Objections***

5. **(Prior Objection- Withdrawn)** Claim 2 was objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. However, claim 2 reads on methods wherein the contacting involves two steps; first, the contacting of a cell with an antibody comprising an epitope tag, and second contacting the cell with a reporter comprising an moiety that binds the epitope tag. In view of the amendments of the claims such that 1) claim 1 does not require that the ligand and reporter be coupled when the ligand is contacted to the cell, and 2) claim 2 does not require any particular order in which the ligand is contacted to the cell relative to its coupling to the reported, the rejection is withdrawn.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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7. **(Prior Rejection- Withdrawn)** Claims 1-3, 5-10, and 12-15 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendments to the claims, the rejection is withdrawn.

8. **(Prior Rejection- Withdrawn)** Claims 1- 3, and 5-15 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendments to the claims, the rejection is withdrawn.

9. **(Prior Rejection- Withdrawn)** Claim 12 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendment of the claim's dependency, the rejection is withdrawn.

10. **(New Rejection- Necessitated by Amendment)** Claim 92 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is rejected because it is unclear what is meant by the phrase "a member cell." It is not clear what such a cell is a member of, or what defines a "member."

Clarification is required.

11. **(New Rejection- Necessitated by Amendment)** Claim 93 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

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distinctly claim the subject matter which applicant regards as the invention. The claim is rejected because it is not clear what is meant by reference to "said cell." The claim depends from claim 87, which refers to a plurality of cells. It is not clear if the "said cell" of claim 92 refers to any of the plurality of cells, or is intended to designate a specific cell from the plurality.

Clarification is required.

***Claim Rejections - 35 USC § 102***

12. **(Prior Rejection- Withdrawn)** Claims 1, 3, 5-7, 10, 13, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6,794,128. The Applicant's arguments in traversal are found persuasive. While the reference teaches the dissociation of non-internalized ligands from the cell, the reference does not teach the dissociation of the non-internalized ligand from the reporter. The rejection is therefore withdrawn.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. **(Prior Rejection- Maintained)** Claims 1, 3, 10, and 13-15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hein et al. (U.S. Patent 6,251,392- of record in the December 2002 IDS) in view of the teachings of Hurwitz et al. (PNAS 92:3353-57- of record in the July

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2003 IDS) and U.S. Patent 5,296,348 (the '348 patent, issued to Rakowicz-Szulczynska). It is noted that, although the embodiments described by claim 5 were described and rejected in the prior action and recognized as rejected by the Applicant as rejected (see e.g., Response page 15, noting the identification of antibodies as the internalized ligands). The claim is therefore now included in the rejection. The rejection is maintained, and extended to claims 77, 78, 81, 83-85, 87-89, 92, and 93.

The Applicant traverses this rejection by asserting that the claims do not teach or suggest the claimed invention wherein the non-covalently coupled reported is dissociated from the non-internalized ligand. More particularly, the Applicant asserts that such a step is not disclosed by the Hein reference (as was acknowledged in the prior action), and that this deficiency is corrected by the teachings of Hurwitz and the '348 patent. This argument in traversal is not found persuasive.

It is acknowledged that the Hurwitz reference teaches the use of non-covalent labels, and therefore does not alone render the claimed limitations obvious. However, the reference nonetheless demonstrates that those in the art were aware of the need to distinguish internalized ligands from those not internalized into the cell. This idea is also demonstrated in the Tsaltas reference. While the Tsaltas reference teaches problems in the use of certain buffers commonly used for dissociation of reporters from ligands, the reference does not teach that the methods themselves are unreliable. Rather, the reference teaches that certain buffers are not uniform in their ability to cause such dissociation, and indicates that those in the art should beware of such when performing assays where such dissociation is required. The teachings of this reference

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merely constitute a caution to those in the art in the choice of wash buffers, but do not constitute a teaching away from the claimed invention.

Further, the use of radiolabelled ligands is not the only means for detecting the internalization described by the two cited references. For example, in column 4 of the '348 patent, the reference teaches the detection of an internalized ligand (a Mab) with a second, labeled, antibody. Thus, the use of a buffer to remove non-internalized antibodies as suggested by the teachings of both Hurwitz and the '348 patent, where the two antibody approach suggested by the '348 patent is used, would also result in the dissociation of the non-internalized Mab and the labeled antibody (thus dissociation of the Mab and the reporter). The combination of these references therefore meets indicated claim limitations. For these reasons, and the reasons of record, the rejection is maintained.

With respect to claims 77 and 78, it is noted that, although the '348 reference teaches the successive addition of the ligand and reporter during the contacting step (col. 4, lines 49-66), it would have been apparent to those in the art that the reporter and ligand may also be coupled prior to the contacting step. This is because those in the art would have recognized that the timing of the conjugation would not be important to the assay so long as the reporter does not interfere with the binding of the ligand to the cell. Further, because the purpose of the identification of such ligands is for the purpose of identifying drug carriers, those in the art would have been interested in the ability of the ligand to bind the cell while attached to additional moieties during the contacting step. The references therefore render the limitations of claims 77 and 78 obvious. The '348 reference also indicates that the reporter may be a



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fluorescent label, and may be detected by fluorescent microscopy. See e.g., columns 7-8. The limitations of claim 81 are therefore met.

Claims 83 and 92 further require the isolation of the cell comprising the internalized ligand. As was indicated in the prior action, the references render obvious the recovery of the internalized ligands from the cells. In order to do so, it would also have been obvious to those in the art to isolate the cells into which the ligands were internalized. The references therefore also render claims 83 and 92 obvious.

Claims 84 and 93 additionally require that the detection of the presence of the reporter comprises a quantification of the reporter present in the cell. In columns 5, the '348 patent suggests the benefits of making a quantitative determination of the internalization of the ligands (i.e., to determine the most efficient transporters). In view of this, and because both the '348 patent (e.g., cols. 4-5) and Hurwitz (col 4) indicate that such measurements are within the skill of those in the art, the making of a quantitative measurement as required by claims 84 and 93 would also have been obvious to those in the art.

Claim 85 additionally teaches that the detection step involves detection both prior to and after the dissociation of the report from the non-internalized ligand. The Hein reference indicates that both the ligands that bind to, and those that are internalized into, target cells are useful. Column 4. Further, the reference indicates that, where those in the art are determining only the binding of the ligand to the cell, the non-internalized ligands need not be separated from the label. However, where the ligand is internalized, those in the art would be required to distinguish between the internalized ligands, and those not brought into the cell. Thus, it would have been obvious to those in the art both to detect the binding of ligand to the cell without dissociating

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non-internalized ligands (i.e. detection prior to dissociation), and then to dissociate ligands- and non-covalently bound ligand labels- from the cells to determine which ligands are internalized. Because the reference indicates that both internalized and non-internalized ligands are useful, and thus suggests the determination of first binding and then internalization (after removing non-internalized reporter), the teachings of the reference render claim 85 obvious.

For these reasons, and the reasons of record, the rejection is maintained and extended to the indicated newly added claims.

15. **(Prior Rejection- Maintained)** Claims 2 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, and further in view of Burner et al. (U.S. Patent 6,087,103) and of Collins (U.S. Patent 5,770,422) and Freed et al. (U.S. Patent 5,597,719). The rejection is further extended to claim 79 and 86. As indicated in the prior action, claim 2 reads on methods such as those described above, except that that the cell is contacted with two separate compounds, the first is the antibody comprising an epitope tag, and the second is a reporter comprising a moiety that binds the epitope tag. The teachings of the Hein, Hurwitz, and the '348 patent have been described above. While these references teach the detection of antibodies using a reporter, they do not teach the use of an epitope tag to link the reporter and the antibody. The Applicant traverses the rejection on the basis that the references do not teach each of the claim limitations. In particular, the Applicant asserts that the references do not teach the dissociation of the reporter from the ligand. Further, the Applicant asserts that the Burner reference does not teach the use of epitope tags.

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The first assertion is not found persuasive for the reasons indicated above with respect to the rejection over Hein, Hurwitz, and the '348 patent. The second assertion is also not found persuasive. The fact that Burner may not teach the use of epitope tags is insufficient to demonstrate that the combination of references cited fails to teach the use of epitope tags. In view of the teachings (as indicated above) the '348 patent and Burner with regards to the use of multiple antibodies, the teachings of Burner indicating that tags may be used to conjugate a detectable moiety to a ligand, and the teachings of Collins and Freed with reference to the use of epitope tags for the conjugation of different moieties, the combination of these references renders obvious the use of such tags to conjugate the ligand to the reporter. The Applicant's arguments in traversal are therefore not found persuasive, and the rejection is maintained.

Claim 79 additionally requires that the method be performed in a microtiter plate. Claim 86 requires that at least 2 different ligands be tested. Based on the teachings of Burner, it would have been obvious to those in the art that a microtiter plate would be beneficially used where several ligands or tags are being tested. See e.g., column 2, lines 22-26, and col. 2 line 57 to col. 3 line 2. These teachings would therefore have rendered obvious the use of microtiter plates as indicated in claim 79, and the parallel tested of multiple ligands as indicated in claim 86. These claims are therefore obvious over the cited references.

16. **(Prior Rejection- Maintained)** Claims 6 and 7 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, and further in view of Barbas et al., PNAS 88:7978-7982) and Ward et al. (J Immunol Methods 189: 73-82). The Applicant traverses the rejection on the same grounds as asserted with respect to claims 1, 3, 10,

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and 13-15 above. The rejection is therefore maintained for the same reasons as were indicated above.

17. **(Prior Rejection- Maintained)** Claims 9-11 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, further in view of the teachings of Plant et al. (U.S. Patent 5,389,523- of record in the July 2003 IDS) and Szoka et al. (U.S. Patent 6,593,308). The Applicant traverses the rejection on the same grounds as asserted with respect to claims 1, 3, 10, and 13-15 above. The rejection is therefore maintained for the same reasons as were indicated above.

18. **(Prior Rejection- Maintained)** Claims 9 and 12 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hein, Hurwitz, and the '348 patent as applied above, further in view of Stewart et al. (U.S. Patent 6,087,452). The Applicant traverses the rejection on the same grounds as asserted with respect to claims 1, 3, 10, and 13-15 above. The rejection is therefore maintained for the same reasons as were indicated above.

### ***Double Patenting***

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

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provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. **(Prior Rejection- Withdrawn)** Claims 1, 3, 5-7, 10, 13, and 14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-12, 23-31, 33-36 of U.S. Patent 6,794,128. This rejection is withdrawn on the same grounds as indicated with respect to the rejection under 102(e) supra.

21. **(Prior Rejection- Withdrawn)** Claims 1, 3, 5-7, 10, 13, and 14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, and 12-15 of U.S. Patent No. 10/855,755. In view of the cancellation of claims 1-7 and 12-15 from the copending application, the rejection is withdrawn.

### ***Conclusion***

22. No claims are allowed.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

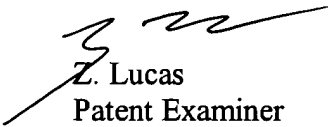
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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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6/13/05